सत्यमेव जयते

INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application, Complete Specification*** *and* ***Drawing Sheets*** *filed in connection with Application for Patent No.**1096/Del/2002** dated 31st **October 2002.***

Witness my hand this 23rd day of December2003.

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

(S.K. PANGASA)
Assistant Controller of Patents & Designs

FORM 1 1095 DEL 02

THE PATENTS ACT, 1970
(39 of 1970)

31 OCT 2002

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"PROCESS FOR THE PREPARATION OF NOVEL AMORPHOUS FORM OF MOXIFLOXACIN HYDROCHLORIDE"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. SUJAY BISWAS

b. PROSENJIT BOSE

c. YATENDRA KUMAR

DUPLICATE

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126, 6342001 – 10
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, SUJAY BISWAS, PROSENJIT BOSE, YATENDRA KUMAR of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. Sujay Biswas

(SUJAY BISWAS)

b. P Bose

(PROSENJIT BOSE)

c. Yatendra Kumar

(YATENDRA KUMAR)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No.655391 dated 28-10-2002 on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **28TH** day of **October, 2002.**

For Ranbaxy Laboratories Limited

Sd/-

(SUSHIL KUMAR PATAWARI)
Company Secretary

FORM 2

The Patents Act, 1970

(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

PROCESS FOR THE PREPARATION OF NOVEL AMORPHOUS FORM OF MOXIFLOXACIN HYDROCHLORIDE

DUPLICATE

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a process for the preparation of novel amorphous form of moxifloxacin hydrochloride.

Moxifloxacin, an 8-methoxyquinolone, has potent bactericidal activity against Gram-positive, Gram-negative and a typical pathogens. It is well known in the literature that moxifloxacin is one of the most active quinolones against bacteria already resistant to penicillins and macrolides. Additionally, moxifloxacin is also useful as feed additives.

Moxifloxacin hydrochloride is chemically, 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7as)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-3-quinoline-carboxylic acid has structural Formula I as shown in the accompanied drawings. Moxifloxacin as well as its addition products are disclosed in US patent No. 4,990,517 assigned to Bayer.

US patent No. 5,607,942 describes that moxifloxacin or an alkali metal, alkaline earth metal, silver or guanidium salt thereof or a pharmaceutically utilizable hydrate or acid addition salts thereof, and moxifloxacin substantially free of other enantiomers and stereoisomers is used as an antibacterial composition.

US Patent No. 5,849,752 discloses novel monohydrate of moxifloxacin in prismatic crystal form. However, there is no teaching of the amorphous form of moxifloxacin hydrochloride in the known prior art.

It is known that different morphs of biologically active compounds may have different absorption profile in vivo and consequently different pharmacokinetic profile.

The difference in the activity of different polymorphic forms of a given drug has drawn the attention of many workers in recent years. This has especially become very interesting after observing that many antibiotics, antibacterials, tranquilizers etc. exhibit polymorphism and some one of the polymorphic forms of a given drug exhibit superior bioavailabiltiy and consequently show much higher activity compared to the polymorphs. The term polymorphism includes different physical forms, crystal forms, crystalline / liquid crystalline / non-crystalline (amorphous) forms.

It has also been disclosed that the amorphous forms in the number of drugs exhibit different dissolution characteristics and in some cases different bioavailability patterns compared to the crystalline form [Konne T. Chem Pharm Bull 38, 2003 (1990)]. For some therapeutic indications one bioavailability pattern may be favoured over another. Cefuroxime axetil is the classical example of amorphous form exhibiting higher bioavailibility than the crystalline form. Host of patents have been granted on a number of drugs exhibiting polymorphism.

The present invention relates to a new form of moxifloxacin hydrochloride, the amorphous form. The new form is characterized by its X-ray powder diffraction spectrum and IR spectrum and can be distinguished from the known anhydrous and crystalline monohydrate forms by comparing the X-ray powder diffraction spectrum and IR spectrum

Accordingly, the present invention provides an amorphous form of moxifloxacin hydrochloride and a process for preparation thereof. The process comprises dissolving moxifloxacin hydrochloride in a suitable solvent(s), water or mixtures thereof and recovering amorphous form and solvent by conventional technique. Such conventional techniques include, but are not limited to distillation, distillation under vacuum, evaporation, spray drying, freeze drying etc.

In a preferred embodiment of the invention moxifloxacin hydrochloride is recovered from solution in an amorphous form using a spray drying technique. The mini-spray dryer (Model : Buchi type) which is used, operates on the principle of nozzle spraying in a parallel flow i.e. spray product and drying gas flow in the same direction. The drying gas can be air or inert gases such as nitrogen, argon and carbon dioxide. Nitrogen is preferred in this case.

The term "suitable solvent" means lower alkanols, ketones, chlorinated solvents or mixtures thereof. Lower alkanols include those primary, secondary and tertiary alcohols having one to six carbon atoms, preferably selected from primary, secondary and tertiary alcohols having one to four carbon atoms such as methanol, ethanol, n-propyl alcohol, iso propyl alcohol, isobutanol, n-butanol, t-butanol or mixtures thereof.

In a more preferred embodiment methanol is used.

The process of the said invention also includes various solvates of moxifloxacin hydrochloride and its conversion to amorphous moxifloxacin hydrochloride.

Figure 1 is an infrared spectrum showing peaks characteristic of amorphous moxifloxacin hydrochloride.

Figure 2 is an X- ray powder diffraction (XRD) pattern of amorphous moxifloxacin hydrochloride.

Figure 3 is an infrared spectrum showing peaks characteristic of crystalline monohydrate form of moxifloxacin hydrochloride obtained per U.S. patent No. 5,849,752 : 3 (A) anhydrous and 3 (B) monohydrate.

Figure 4 is an XRD pattern characteristic of crystalline monohydrate form of moxifloxacin hydrochloride obtained per U.S. patent No. 5,849,752. 4 (A) anhydrous and 4 (B) monohydrate.

Figure 2 shows no peak which are characteristic of crystalline moxifloxacin hydrochloride (Figure 4 of the accompanied drawings) showing the form to be an amorphous one.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

EXAMPLE

A suspension was made from crystalline moxifloxacin hydrochloride (20 g) in methanol (600 ml) at ambient temperature. The resulting solution was slowly heated to 40-42°C for 30 minutes to get a clear solution which was subjected to spray drying on 190 Mini Spray Dryer (Buchi make) at a temperature of 67-68°C using nitrogen gas. The moxifloxacin hydrochloride in an amorphous form was collected. It was further dried at 50-55°C for 10 hours under vacuum to yield amorphous moxifloxacin hydrochloride.

X- ray powder diffraction (XRD) pattern (Figure 2) does not exhibit any peak and shows a plain halo thus demonstrating the amorphous nature of the product. Infrared spectrum in KBr (Figure 1) is different than one obtained for crystalline form of moxifloxacin hydrochloride.

WE CLAIM :

1. A process for the preparation of moxifloxacin hydrochloride in amorphous form which comprises dissolving moxifloxacin hydrochloride in suitable solvent(s), water or mixtures thereof and recovering the amorphous form of moxifloxacin hydrochloride.

2. The process of claim 1 wherein suitable solvent(s) is selected from lower alkanols, ketones, chlorinated solvents or mixtures thereof.

3. The process of claim 2 wherein lower alkanols includes primary, secondary and tertiary alcohols having from one to six carbon atoms.

4. The process of claim 2 wherein lower alkanols includes primary, secondary and tertiary alcohols having from one to four carbon atoms.

5. The process of claim 4 wherein lower alkanols is selected from methanol, ethanol, n-propyl alcohol, iso propyl alcohol, isobutanol, n-butanol, t-butanol or mixtures thereof.

6. The process of claim 5 wherein the solvent is methanol.

7. The process of claim 1 wherein the solvent is removed by a conventional technique.

8. The process of claim 7 wherein the conventional technique includes distillation, distillation under vacuum, evaporation, spray drying or freeze drying

9. The process of claim 8 wherein moxifloxacin hydrochloride in an amorphous form is recovered by spray drying.

10. The process of claim 9 wherein the spray drying is effected in the presence of nitrogen gas.

11. A process for the preparation of moxifloxacin hydrochloride in amorphous form of structural formula I shown in the accompanied drawings substantially described herein and exemplified by the example.

Dated this 30TH day of **October, 2002.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

Ranbaxy Laboratories Limited

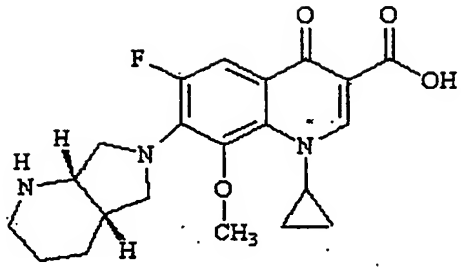
Application No.

No. of sheets = 05

Sheet 01 of 05

1090 DEL 02

31 OCT 2002



.HCl

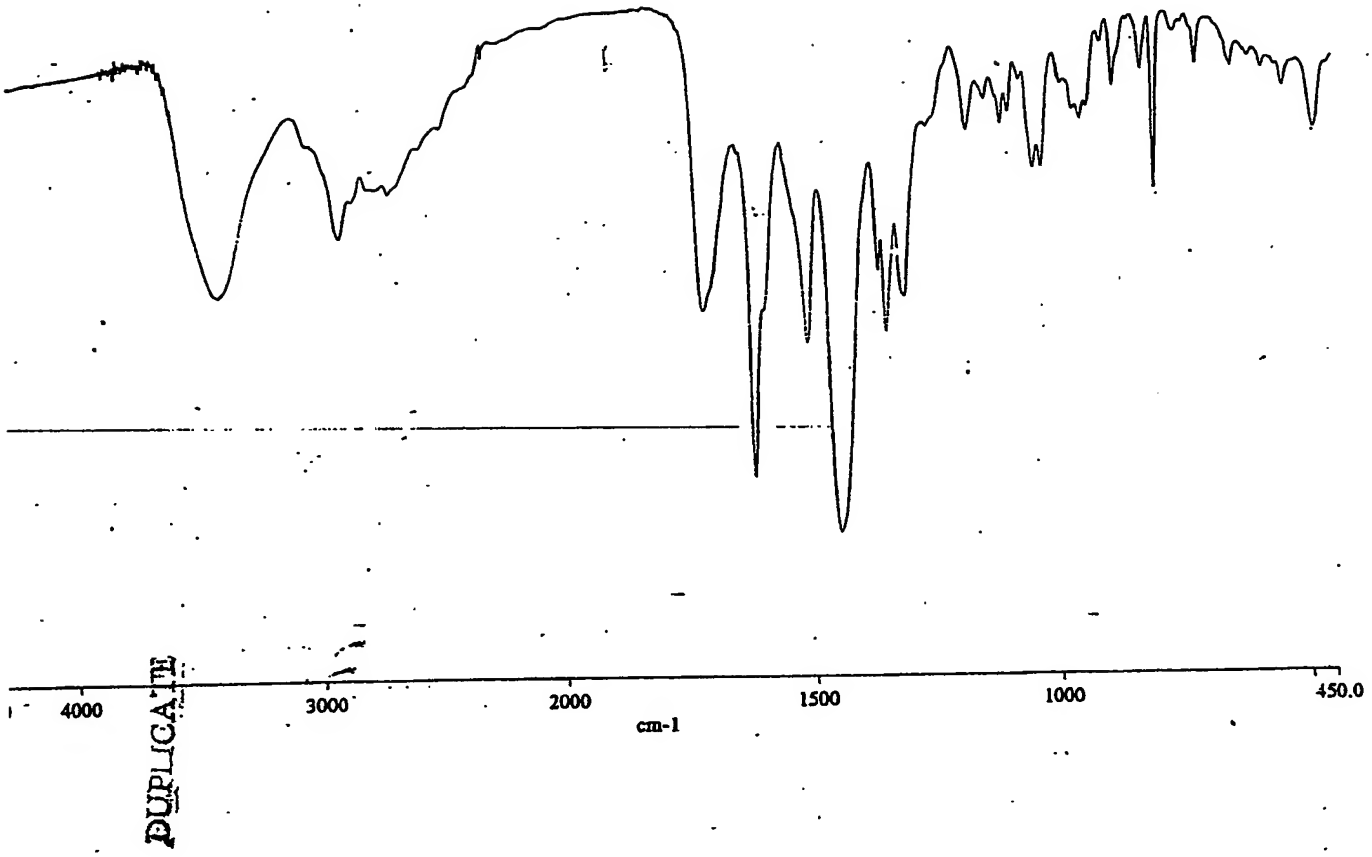
FORMULA I

DUPLICATE

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

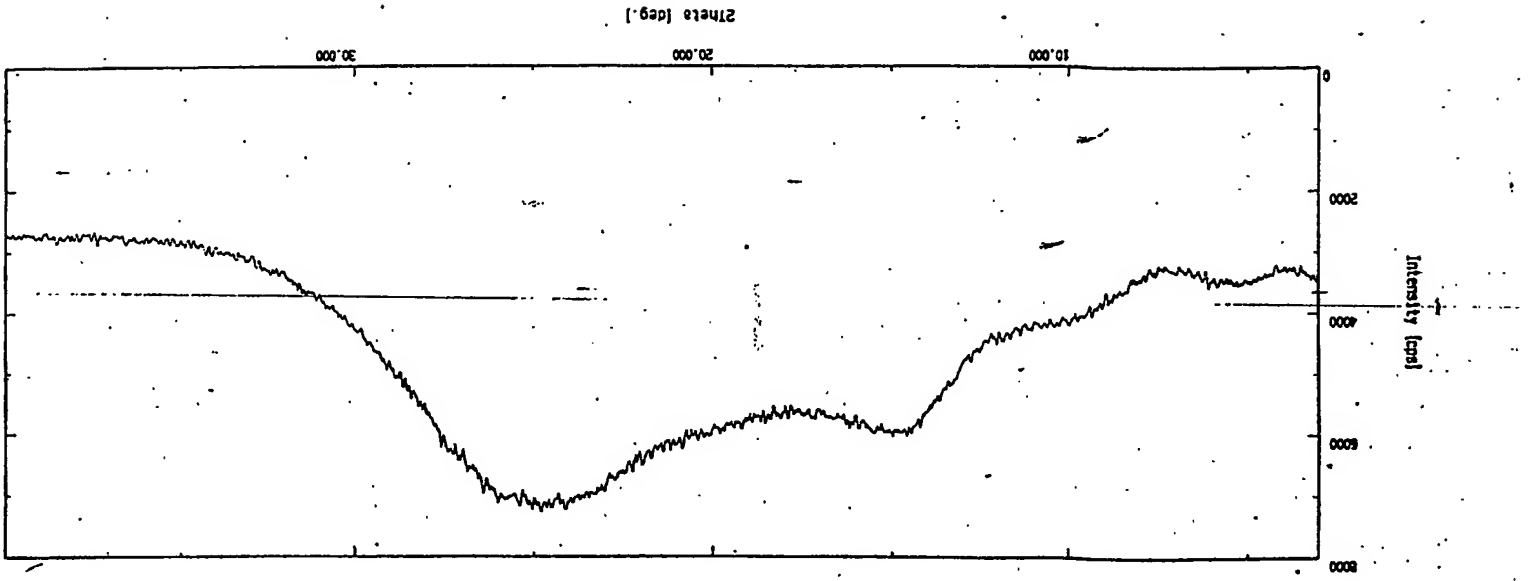
FIGURE 1



For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

FIGURE 2



For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

FIGURE 3

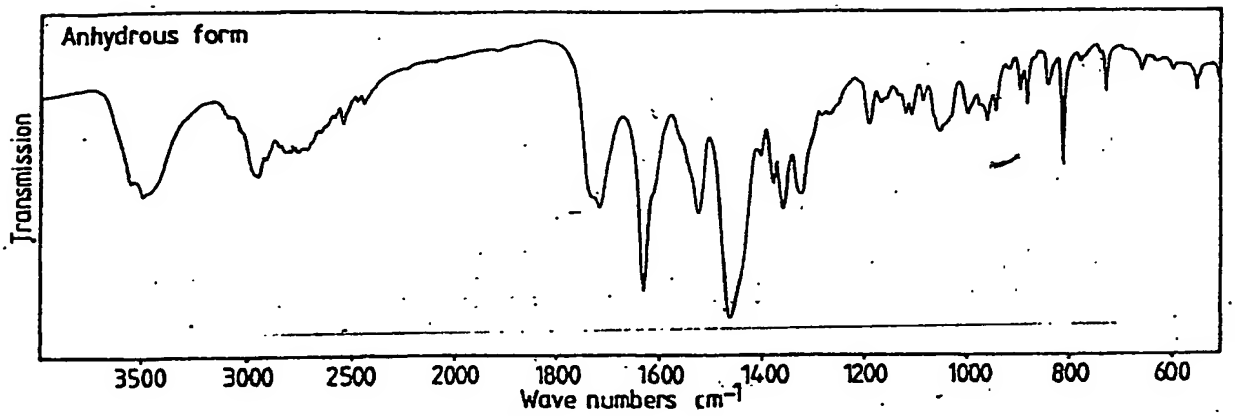


FIG.3A

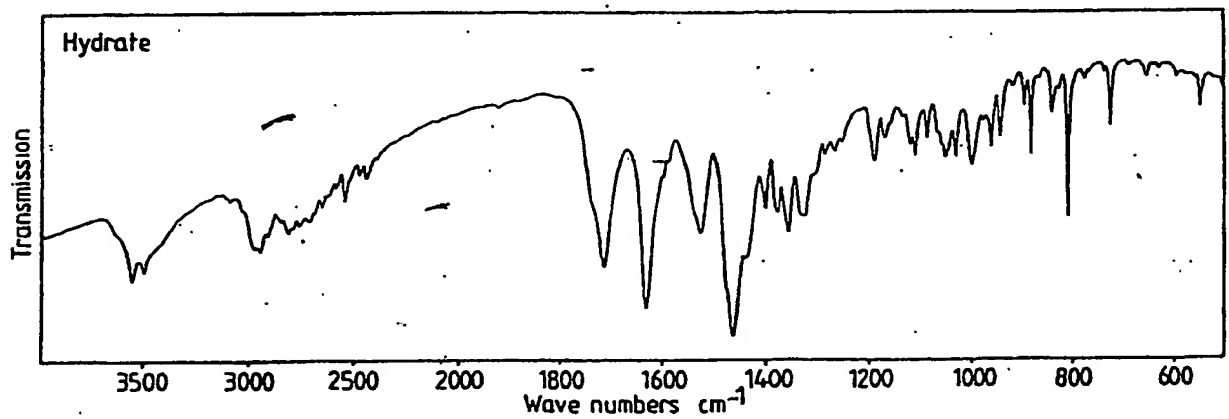


FIG.3B

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

FIGURE 4

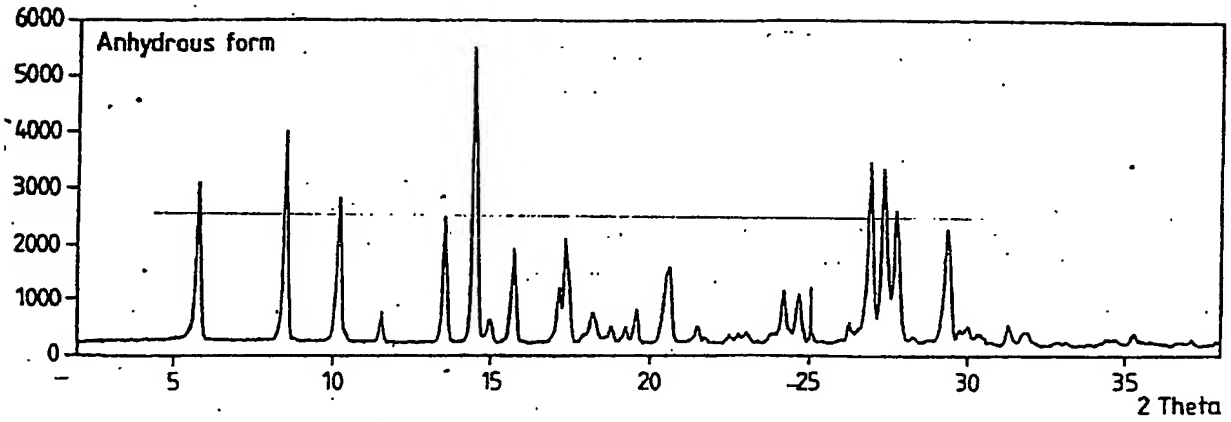


FIG. 4A

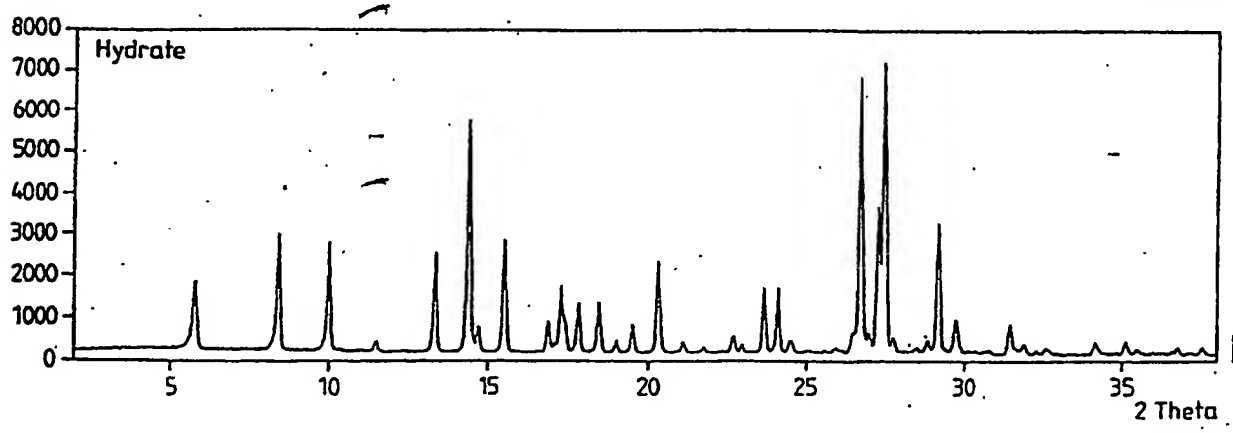


FIG. 4B

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